CHRONIC TOXICITY SUMMARY

DI(2-ETHYLHEXYL)PHTHALATE

(DEHP; Bis-(2-ethylhexyl)phthalate: BEHP; 1,2-benzenedicarboxylic acid; bis(ethylhexyl)ester)

CAS Registry Number: 117-81-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**10 µg/m^3**
Critical effect(s)	Increased liver weight with the appearance of lung alveolar thickening and foam-cell proliferation in rats
Hazard index target(s)	Alimentary system; respiratory system

II. Physical and Chemical Properties Summary (HSDB, 1995)

Molecular formula	$C_{24}H_{38}O_4$
Molecular weight	390.54 g/mol
Description	colorless to light colored liquid
Vapor pressure	1.32 mm Hg at 200^{o}C
Solubility	<0.01% in water; miscible with mineral oil and hexane
Conversion factor	1 ppm = 15.97 mg/m^3 at 25 ^{o}C

III. Major Uses and Sources

Di(2-ethylhexyl)phthalate (DEHP) is predominantly used as a plasticizer for polyvinyl chloride (PVC) and vinyl chloride resins. Plastics derived from these compounds may contain up to 40% DEHP. Plasticizers increase the flexibility of PVC for use in many items such as toys, vinyl upholstery, adhesives, coatings, and as components of paper or paperboard. Polyvinyl chloride is also used to produce disposable medical and surgical gloves, and the flexible tubing used for blood transfusions, hemodialysis, and parenteral solutions (HSDB, 1995).

IV. Effects of Human Exposure

No studies have investigated the toxic effects of DEHP in humans after chronic inhalation exposure. Limited medical case studies have discussed the potential for adverse effects due to DEHP exposure from respiratory tubing systems (Roth *et al.*, 1988) or hemodialysis equipment (Ganning *et al.*, 1984; Woodward, 1990). In one case study, a dialysis patient had an increased number of liver peroxisomes after 1 year, but not after 1 month of treatment (Ganning *et al.*,

1984). Patients on long-term dialysis may be at risk for polycystic kidney disease, with DEHP postulated as a possible causative agent; however, there are insufficient data to confirm a causative role (Woodward, 1990).

V. Effects of Animal Exposure

Experimental data on the inhalation toxicity of DEHP is very limited. The majority of studies have focused on oral exposure to DEHP (reviewed in USDHHS, 1993). Oral exposure to DEHP causes liver enlargement and peroxisome proliferation in rodents at levels down to 10 mg/kg/day DEHP. Humans, other primates, and hamsters are considered more resistant to such oral DEHP exposure related hepatomegaly and peroxisome proliferation (Butterworth *et al.*, 1989; Ganning *et al.*, 1991; Rhodes *et al.*, 1987; Short *et al.*, 1987). Oral exposure to DEHP also produces adverse reproductive and developmental effects in rodents, including decreased maternal body weight, decreased fetal weight, increased fetotoxicity and fetal malformation (Tyl *et al.*, 1988).

Schmezer *et al.* (1988) conducted a chronic inhalation study in Syrian Golden hamsters to evaluate the carcinogenic potential of DEHP (mortality and tumor incidence). No treatment related differences in survival or carcinogenicity were observed after 23 months exposure to 0.015 mg/m^3 DEHP (free-standing NOAEL). Extremely limited histopathological and systemic endpoints, and no clinical chemistry data were evaluated. The single DEHP inhalation dose evaluated (0.015 mg/m^3) corresponds to the highest concentration at which aerosol formation due to condensation is prohibited and to an approximate oral dose of 7 to 10 mg/kg/day (investigators' calculation).

One intermediate duration study of inhaled DEHP aerosols in rats identified a LOAEL of 1000 mg/m^3 (62.6 ppm) for increased liver weights (males and females), lung weights (males) and foam cell proliferation (males) after 4 weeks of exposure (Klimisch *et al.*, 1992). Animals were exposed (head and nose) to respirable particle size aerosol concentrations of 0, 10, 50 or 1000 mg/m^3 DEHP (mass median aerodynamic diameter < 1.2 μm) 6 hours/day for 4 weeks. All these treatment related effects appeared to reverse after a 8 week post-exposure period. Additionally, this study included a fertility assessment. DEHP exposure did not impact mating performance and male fertility after two matings of treated males with untreated females.

The only other inhalation study evaluated the developmental toxicity of DEHP in Wistar rats following an acute 10 day exposure (Merkle *et al.*, 1988). In an initial range finding experiment, dams exposed to 0, 200, 500 or 1000 mg/m^3 DEHP for 6 hours/day demonstrated an increasing trend in hepatic peroxisome proliferation. A second group of dams was then exposed to 0, 10, 50 or 300 mg/m^3 DEHP 6 hours/day for 10 days. No treatment related pre- or postnatal mortality or developmental effects were observed. The developmental study design limited the number of systemic endpoints evaluated.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Klimisch *et al.* (1992)
Study population	Wistar rats (27 males & 17 females/group)
Exposure method	Discontinuous whole-body inhalation exposure (0, 10, 50, or 1000 mg/m^3)
Critical Effects	Increased liver weight and lung weight with the appearance of lung alveolar thickening and foam-cell proliferation
LOAEL	1000 mg/m^3
NOAEL	50 mg/m^3
Exposure continuity	6 hrs/day, 5 days /week
Average experimental exposure	8.9 mg/m^3 for NOAEL group
Human equivalent concentration	3.4 mg/m^3 for NOAEL group (particulate with pulmonary respiratory effects, female rat RDDR = 0.38, based on MMAD = 1.0 µm, sigma g = 2.63, BW = 156 g, MV = 0.12 L/min, SA(ET) = 15 cm^2)
Exposure duration	4 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.01 mg/m^3 (10 $\mu g/m^3$)

Of the three DEHP inhalation studies available, only Klimisch *et al.*, (1992) determined a NOAEL and LOAEL for the critical effects: increases in liver weight and lung weight with the appearance of lung alveolar thickening and foam-cell proliferation. Histopathological analysis was done at the end of DEHP exposure and in a smaller group after 8 weeks recovery post-exposure. The critical adverse liver effects identified (significant increases in absolute and relative liver weight) were similar to those seen in the more abundant oral DEHP rodent studies. However, this organ weight increase was not accompanied by histological effects, a pattern seen in oral DEHP studies (Woodward, 1988). Neither peroxisome proliferation nor alterations in plasma cholesterol levels were observed, even at the highest exposure level (1000 mg/m^3). The one other shorter term, 10 day, DEHP inhalation study in rats identified a NOAEL of 300 mg/m^3 for hepatic peroxisome proliferation (Merkle *et al.*, 1988), an exposure level falling between the principal study's NOAEL (50 mg/m^3) and LOAEL (1000 mg/m^3).

The adverse respiratory effects, increases in relative lung weight accompanied by foam cell proliferation and thickening of alveolar septa, have not been described in other DEHP studies following oral exposure (Klimisch et al., 1992). However after intravenous administration, DEHP and its hydrolysis product mono(2-ethylhexyl)phthalate (MEHP) accumulated in the lungs of rats. Pulmonary hemorrhage and inflammation were followed by death in this acute study (Schulz *et al.*, 1975). One medical study on three preterm infants identified pulmonary edema and bronchial asthma resembling hyaline membrane disease following artificial ventilation with

DEHP-containing PVC respiratory tubes emphasizing the potential for adverse lung effects following inhalation of DEHP (Roth *et al.*, 1988).

Additionally, adverse renal effects including increases in kidney weight, focal cystic changes, decreased creatinine clearance and accumulation of lipofuscin deposits in tubular cells (Rao *et al.*, 1990), although often identified in chronic oral DEHP studies, were not identified in this principal study (Klimisch *et al.*, 1992). The possible exposure to DEHP through kidney dialysis has been discussed as a potential negative effect on the human kidney (Woodward, 1990).

No epidemiological data exist relating DEHP exposure to any adverse inhalation or chronic systemic effects. The few medical case studies available describe the potential for adverse effects, but lack sufficient data to allow for correlation of dose and response, or any exposure parameters to reach conclusions concerning cause-and-effect.

The paucity of human (inhalation or oral) and animal data (inhalation) on the adverse effects of DEHP exposure lends a high degree of uncertainty to the chronic REL determination. The vast majority of animal studies have been conducted in rodent species using oral routes of exposure. Though the liver appears the critical target organ in rodents, with hepatomegaly and peroxisome proliferation being the two most common adverse endpoints, nonrodent species appear less susceptible to peroxide production by peroxisomes after exposure to DEHP (Butterworth *et al.*, 1989; Ganning *et al.*, 1991; Rhodes *et al.*, 1987; Short *et al.*, 1987).

The strengths of the inhalation REL include the availability of inhalation exposure data from a well-conducted study with histopathological analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the lack of chronic inhalation exposure studies.

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CHRONIC TOXICITY SUMMARY

1,4-DICHLOROBENZENE

(p-Dichlorobenzene; di-chloricide; p-dichlorobenzol; Paradow; Paramoth; Parazene; p-chlorophenyl chloride)

CAS Registry Number: 106-46-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**800 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	General effects (Reduced body weights and food consumption) in rats CNS effects (tremors) in rats Respiratory/dermal effects (nasal and ocular discharge) in rats Liver effects (increased liver weight) in rats, and Kidney effects (increased kidney weight) in rats.
Hazard index target(s)	Nervous system; respiratory system; alimentary system; kidney

II. Chemical Property Summary (HSDB, 1994)

Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01 g/mol
Description	White crystals, monoclinic prisms
Vapor pressure	10 mm Hg atm @ 54.8 ^oC
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	6.0 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Commercial grade 1,4-dichlorobenzene (1,4-DCB) is available in the USA as a technical grade liquid, typically containing a small percentage (>0.1% by weight) of meta and ortho isomers; as a solution in solvent or oil suspension; or as crystalline material pressed into various forms (HSDB, 1994). Besides its role as an intermediate in the synthesis of various organics, dyes and pharmaceuticals, 1,4-dichlorobenzene is used as a space or garbage deodorizer for odor control. The insecticidal and germicidal properties of 1,4-dichlorobenzene are utilized to control fruit

borers and ants; moths; blue mold in tobacco seed beds; and mildew and mold on leather or fabrics.

IV. Effects of Human Exposure

Case reports of humans exposure to 1,4-DCB include malaise, nausea, hepatic manifestations (yellow atrophy and cirrhosis), proteinuria, bilirubinuria, hematuria, and anemia. A woman exposed to 1,4-DCB for 6 years developed central nervous system effects, including severe cerebellar ataxia, dysarthria, weakness in all limbs, and hyporeflexia (U.S. EPA, 1985).

No epidemiologic studies of 1,4-DCB exposures were located.

V. Effects of Animal Exposure

CNS effects have been observed in rats, rabbits and guinea pigs exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/m^3) of 1,4-DCB by inhalation 7 hours/day, 5 days/week for 6-7 months (Hollingsworth *et al.*, 1956). High dose animals showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Observed liver and kidney changes included cloudy swelling and centrilobular cellular degeneration (liver). One other inhalation study in rats exposed to 0, 75 or 500 ppm (0, 451 or 3006 mg/m^3) for 5 hours/day, 5 days/week for 76 weeks (Riley *et al.*, 1980) found increased kidney and liver weights in the high dose group, 16% at 26 weeks, 33% at 76 weeks, and 10% at 32 weeks post-exposure. Additionally, studies with oral exposure to 1,4-DCB, including the NTP (1987) chronic bioassay study (maximum dose 300 mg/kg-day), have found an increased incidence of renal and hepatic lesions (cellular degeneration and focal necrosis).

Three inhalation reproductive studies, one in rabbits (Hayes *et al.*, 1985), one in mice (Anderson and Hodge, 1976), and one in rats (Chlorobenzene Producers Assn., 1986), found minimal reproductive effects. In rabbits exposed to 800 ppm (4810 mg/m^3) 1,4-DCB on days 6-18 of gestation, only the difference in percentage of implantations reabsorbed and percentage of litters with resorptions for the 300 ppm group were significant (Hayes *et al.*, 1985). No reduction in reproductive performance was observed in mice exposed to 0, 75, 225, or 450 ppm 1,4-DCB for 6 hours/day for 5 days (Anderson and Hodge, 1976).

In a two-generation reproductive study, Sprague-Dawley rats P1 (28/sex/group) were exposed to 0, 50, 150 or 450 ppm (0, 301, 902, 2705 mg/m^3) of 1,4-DCB vapor for 10 weeks, 6 hours/day, 7 days/week, then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks then mated. No developmental abnormalities were observed in pups examined. At 450 ppm a significant decrease in live births, pup weights, and pup survival were seen in both the F1 and F2 generations. Nonreproductive effects observed in the parental males in the 150 and 450 ppm groups included significantly increased liver and kidney weights (Chlorobenzene Producers Association, 1986). All dose levels caused hyaline droplet nephrosis in post-pubescent males; but, this change was associated with the formation of alpha-2u-globulin,

an abnormality considered specific for male rats with no relative human significance (U.S. EPA, 1991). The Chlorobenzene Producers Association reproductive study was chosen by the U.S. EPA to derive an RfC.

VI. Derivation of U.S. EPA Reference Concentration

Study	Chlorobenzene Producers Association, 1986 (evaluated by U.S. EPA, 1994)
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm) over 10 weeks
Critical effects	Reduced body weights and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hr/day for 7 days/week
Average experimental exposure	13 ppm for NOAEL group
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	10 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 ppb, 0.8 mg/m^3, 800 µg/m^3)

A 3-fold subchronic uncertainty factor was used because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980).

The major strengths of the REL are the observation of a NOAEL and the demonstration of a dose-response relationship. The major uncertainties are the lack of human data and the lack of chronic, multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

DICHLORODIFLUOROMETHANE

(Freon 12; fluorocarbon-12; FC 12; CFC-12; Halon)

CAS Registry Number: 75-71-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1,000 μg/m^3**
Critical effect(s)	Liver necrosis and fatty degeneration in guinea pigs
Hazard index target (s)	Alimentary system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	CCl_2F_2
Molecular weight	120.91
Description	Colorless denser-than-air gas; nearly odorless; faint, ether-like odor at high concentrations.
Vapor pressure	84.8 psia at 70 degrees F.
Solubility	Practically insoluble in water (0.28 g/l water @ 25°C @ 1 atm). Soluble in alcohol and ether.
Conversion factor	4.95 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

The reported total demand for all chlorofluorocarbons (CFCs) in the USA in 1985 was 458,000 tons (WHO, 1990). The three major CFCs in 1985, Freon 11, Freon 12 and Freon 113, accounted for 83% of the total CFCs produced in the USA. Major uses of Freon 12 are as a blowing agent for cellular polymers, refrigerant, solvent in paints, varnish removers and polymerization processes, aerosol propellant, leak-detecting agent, food and tissue freezant and as a sterling gas. The compound may also be used in purification of aluminum and copper. Freon 12 is the most widely used refrigerant in the US. However, many of its uses are becoming increasingly restricted or banned (particularly as an aerosol propellant) due to its action as a stratospheric ozone depleter. According to the Montreal Protocol, fully halogenated CFC production in industrialized countries, including Freon 12, will end by Jan. 1, 1996. All of the Freon 12 that is produced will eventually be released to the environment as emissions. General population exposure occurs by inhalation in ambient air. Occupational exposure occurs via inhalation and dermal contact.

IV. Effects of Human Exposures

The kinetics and metabolism of CFCs, including Freon 12, are characterized by rapid pulmonary absorption and distribution. There is no indication of any bioaccumulation. Metabolic transformation of Freon 12 and other similar CFCs is negligible, if it occurs at all. Therefore, toxic effects of metabolites are very unlikely. Regardless of the route of entry, CFCs appear to be eliminated almost entirely through the respiratory tract (WHO, 1990; Mergner *et al.*, 1975).

The known human health effects primarily involve impairment of neurological and cognitive functions and possibly of the cardiovascular system following acute exposure (WHO, 1990). In human volunteers, inhalation of 10,000 ppm of Freon 12 for 2.5 hr caused a 7% reduction in standardized psychomotor scores (Azar *et al.*, 1972). At a concentration of 1000 ppm for 8 hr/day, 5 days/week for a total of 17 repetitive exposures, there were no untoward subjective responses and no abnormal physiological responses of lungs or the heart (Stewart *et al.*, 1978).

In occupational studies of 539 workers exposed to mainly Freon 12 during construction and repairing of refrigeration equipment for up to 10 years, no increase in death rates was seen (Szmidt *et al.*, 1981). In another study, 89 workers were examined during their work with refrigerant equipment involving mainly Freon 12. No effects were seen regarding cardiac arrythmias and reaction time measurements (Edling and Olsen, 1988).

V. Effects of Animal Exposures

The pharmacokinetics of CFCs in laboratory animals, including Freon 12, are similar to that seen in man (WHO, 1990; Blake and Mergner, 1974).

In subchronic studies, Prendergast *et al.* (1967) noted fatty degeneration and necrosis in the liver of guinea pigs following continuous Freon 12 exposure at 4.02 g/m^3 (800 ppm) for 90 days. However, rats, rabbits, dogs and monkeys showed no liver changes from the same dose regimen. Ninety-day exposure (6 hr/day) of dogs to Freon 12 at 25.1 g/m^3 (5000 ppm) and rats at 50.3 g/m^3 (10,000 ppm) was without toxic effect (Leuschner *et al.*, 1983). Clayton (1967) fed Freon 12 in diet at a dose level ranging from 160-379 mg/kg per day to rats and 84-95 mg/kg per day to dogs for approximately 12 weeks. No adverse effects related to nutritional, clinical, laboratory or histopathological indices were found.

The most comprehensive long-term toxicity study with Freon 12 was performed with rats and dogs by Haskell Laboratory (Sherman, 1974). Freon 12 was orally administered (by gavage in corn oil) to 50 rats/sex/group at approximate dose levels of 0, 0 (two control groups), 15 and 150 mg/kg body wt-day (corresponding to dietary levels of approximately 0, 0, 300 and 3000 ppm, respectively) for two years, starting with the offspring of rats that had been given the same compound at the same dose levels for three months. Except for a slightly decreased rate of weight gain (about 10-20% in females and about 10% in males) in those rats that received the

higher dose level of Freon 12, there was no clinical, biochemical, hematological, or histopathologic evidence of toxicity either during or at the end of the study in both exposure groups. A three-generation reproduction study carried out at the same time did not find any adverse findings in any of the indices of reproduction and lactation, including fertility index, gestation index, viability index and lactation index.

The second part of the study investigated the chronic effects of Freon 12 on beagle dogs. Four dogs/sex/group were fed 0, 300 or 3000 ppm of Freon 12 in their diets for two years. No nutritional, hematological, urine analytical, biochemical or histopathologic evidence of toxicity was observed.

A long-term inhalation study in mice and dogs investigated mixtures of CFCs, including 49% Freon 12 (Smith and Case, 1973). Mice were exposed to 0 or 970 mg/kg (calculated value) 5 days/week for 23 months. No signs of toxicity were observed. Adult dogs (three male, three female) were exposed to 0 or 2240 mg/kg (calculated value) per day for 1 year. Other than transient slight drowsiness immediately after dosing, no treatment related effects were found.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Prendergast, 1967
Study population	Guinea pigs
Exposure method	Whole-body inhalation exposures
Critical effects	Liver necrosis and fatty degeneration
LOAEL	800 ppm
NOAEL	Not observed
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	800 ppm for LOAEL group
LOAEL uncertainty factor	10
Subchronic uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	3,000 (maximal uncertainty factor due to lack of independence of the 4 areas of uncertainty (USEPA, 1994))
Inhalation reference exposure level	0.3 ppm (300 ppb; 1 mg/m^3; 1,000 μg/m^3)

In the inhalation study by Prendergast *et al.* (1967), fatty degeneration and necrosis of the liver were observed in guinea pigs following 90 day exposure to 800 ppm Freon 12. As with other CFCs, the pharmacokinetics of Freon 12 is similar in humans and experimental animals. Freon 12 has a rapid half-life upon cessation of exposure with little or no metabolism. No chronic effects have been found in humans and only mild effects noted in experimental animals following chronic exposure to Freon 12.

The strengths of the inhalation REL include the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of observation of a NOAEL, the lack of chronic, multiple-dose health effects data, and the lack of developmental toxicity studies.

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EPA/600/8-90/066F.

CHRONIC TOXICITY SUMMARY

1,1-DICHLOROETHYLENE

(Synonym DCE; 1,1-dichloroethene; VDC; vinylidene chloride)

CAS Registry Number: 73-35-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Critical effect(s)	Increased mortality; hepatic effects (mottled livers and increases in liver enzymes) in guinea pigs
Hazard index target(s)	Alimentary system

II. Physical and Chemical Properties (HSDB, 1995)

Molecular formula	$C_2H_2Cl_2$
Molecular weight	96.95 g/mol
Description	Colorless liquid
Vapor pressure	500 mm Hg @ 20 ^oC
Solubility	Soluble in water (2.5 g/l); miscible in organic solvents
Conversion factor	3.97 μg/m^3 per ppb at 25 ^oC

III. Major Uses and Sources

1,1-Dichloroethene (1,1-DCE) is used in the production of polyvinylidene chloride copolymers (HSDB, 1994). 1,1-DCE containing copolymers include other compounds such as acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate. These copolymers are utilized in flexible packaging materials; as flame retardant coatings for fiber, carpet backing, and piping; as coating for steel pipes; and, in adhesive applications. Flexible films for food packaging, such as SARAN and VELON wraps, utilize such polyvinylidene chloride copolymers.

IV. Effects of Human Exposure

Limited information exists regarding the human health effects following exposure to 1,1-DCE. A few case reports and mortality studies have reported hepatotoxicity and nephrotoxicity after repeated, low-level exposures (EPA, 1976; Ott *et al.*, 1976). However, these investigations were conducted in industrial settings with the possibility of mixed chemical exposures. In preliminary clinical findings reported by the EPA (1976), workers exposed to 1,1-DCE for 6 years or less had a high incidence of hepatotoxicity, with liver scans and measurements of liver enzymes revealing

50% or greater loss in liver function in 27 of 46 exposed workers. Unfortunately, no follow-up study was reported.

V. Effects of Animal Exposure

Several studies have reported on the subchronic or chronic toxicity of 1,1-DCE in laboratory animals exposed either via oral or inhalation routes. The liver is the primary target organ of 1,1-DCE toxicity following acute or chronic inhalation exposure, marked by both biochemical changes (alterations in serum enzyme levels) and histological changes (e.g. midzonal and centrilobular swelling, degeneration, and necrosis) (Gage, 1970; Lee *et al.*, 1977; Plummer *et al.*, 1990; Quast, 1976; Quast *et al.*, 1986). Unfortunately, these longer term studies were limited by studying only one or two doses, or a limited number of animals.

Male and female rats exposed intermittently (6 hours/day, 5 days/week) to 125 or 200 ppm 1,1-DCE over 30 days exhibited centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976, as cited by USDHHS, 1994). Two other studies identified hepatic changes in rats at lower concentrations of 1,1-DCE (6 hours/day, 5 days/week), cytoplasmic vacuolation after 30- or 90-day exposure to 25 or 75 ppm 1,1-DCE (Balmer *et al.*, 1976, as cited by USDHHS, 1994) and, fatty changes after 6 months at 25 ppm 1,1-DCE (Quast *et al.*, 1986).

Laboratory animals appear less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. Beagle dogs exposed to 100 ppm 1,1-DCE for 8 hours/day, 5 days/week for 42 days had no evidence of hepatotoxicity, but continuous exposure to 48 ppm for 90 days caused liver changes (Prendergast *et al.*, 1967). Similarly, monkeys continuously exposed to 48 ppm for 90 days exhibited focal necrosis and hemosiderin deposition, while no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-DCE (Prendergast *et al.*, 1967). Guinea pigs exposed to 1,1-DCE for 24 hours per day for 90 days (0, 5, 15, 25, or 48 ppm) displayed mottled livers at 15 ppm, and increased liver enzyme levels (SGPT and AP) at 48 ppm, for a NOAEL of 5 ppm based on liver changes (Prendergast *et al.*, 1967).

Additional adverse effects observed to a lesser extent in laboratory animals include respiratory and renal toxicity. Nephrotoxicty observed following chronic 1,1-DCE exposure included gross organ (increases in kidney weight) (Klimisch *et al.*, 1979; Quast *et al.*, 1986) and histological changes (tubular swelling, degeneration, and necrosis) (Klimisch *et al.*, 1979; Lee *et al.*, 1977; Prendergast *et al.*, 1967). Rats continuously exposed to 48 ppm 1,1-DCE for 90 days caused nuclear hypertrophy of the renal tubular epithelium (Prendergast *et al.*, 1976). And, mice exposed to 25 ppm 1,1-DCE 4 hours/day, 4 or 5 days/week, for 52 weeks displayed severe tubular nephrotoxicity (Maltoni *et al.*, 1985 as cited by USDHHS, 1994). Though nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage 1970), no respiratory effects were attributed to 1,1-DCE exposure in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm intermittently for 6 weeks (Prendergast *et al.*, 1967) or in rats exposed to 75 ppm for 18 months (Quast *et al.*, 1986).

Toxicokinetic studies in laboratory animals have demonstrated that 1,1-DCE is readily absorbed and rapidly distributed following inhalation exposure (Dallas *et al.*, 1983; McKenna *et al.*, 1978b). Following inhalation exposure to radio-labeled 1,1-DCE, rats preferentially accumulate radioactivity in the kidney and liver (McKenna *et al.*, 1978b; Jaeger 1997a). Glutathione (GSH) conjugation appears the major detoxification route for 1,1-DCE intermediates, and GSH-depleting experimental states, such as drugs and fasting, may tend to increase 1,1-DCE toxicity (Jaeger, 1977; McKenna *et al.*, 1978; Reichert *et al.*, 1978). One study greatly increased 1,1-DCE induced lethality and hepatotoxicity in rats by pretreatment with acetaminophen (Wright and Moore, 1991).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Prendergast *et al.* (1967)
Study population	Guinea pigs (15 per group, except 45 animals in 5 ppm group)
Exposure method	Continuous whole body inhalation (0, 20, 61, 101, or 189 mg/m^3)
Critical effects	Increased mortality at 61 to 189 mg/m^3; hepatic effects (mottled livers and increases in SGPT and AP enzymes) noted at 189 mg/m^3
LOAEL	61 mg/m^3
NOAEL	20 mg/m^3
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	20 mg/m^3 for NOAEL group
LOAEL factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.02 mg/m^3 (20 µg/m^3; 0.005 ppm; 5 ppb)

The principal study (Prendergast *et al.*, 1967) identified adverse hepatic and/or renal effects in rats (15 or 45/group), guinea pigs (15 or 45/group), dogs (2 or 6/group), and monkeys (3, 9, or 21/group) exposed to inhaled 1,1-DCE. Continuous exposure to 1,1-DCE, 24 hours/day over 90 days, demonstrated more severe effects than intermittent exposure, 6 hours/day, 5 days/week for 6 weeks, in the species tested. Unlike the other available subchronic and chronic studies, this principal study included multiple exposure levels of 1,1-DCE, 0, 5, 15, 25 or 48 ppm (0, 20, 61, 101, or 189 mg/m^3). Mortality, hematologic and body weight data were well tabulated and presented in this study. Histopathologic evaluation was conducted on the heart, lung, liver, spleen and kidneys. Following continuous exposure adverse hepatic effects observed included focal necrosis in monkeys (LOAEL 48 ppm, NOAEL 25 ppm), in dogs (LOAEL 48 ppm, NOAEL 25 ppm), in rats (LOAEL 48, NOAEL 25 ppm); and, altered lipid content and increases in SGPT and alkaline phosphatase in guinea pigs (LOAEL 48 ppm, NOAEL 5 ppm).

Additionally, renal alterations were observed in rats as nuclear hypertrophy in the tubular epithelium (LOAEL 48 ppm, NOAEL 15 ppm). Monkeys exposed to 1,1-DCE also displayed a greater than 25% decrease in body weight (LOAEL 48 ppm, NOAEL 5 ppm). The subchronic Prendergast *et al.* (1967) study was chosen over the chronic studies because of its better design its use of continuous exposure, and its exhibition of toxic effects below the LOAELs reported in the other studies.

Though limited in number, the other chronic and subchronic studies available consistently demonstrate adverse hepatic effects following 1,1-DCE exposure (Lee *et al.*, 1977; Maltoni *et al.*, 1985; Plummer *et al.*, 1990; Quast *et al.*, 1986). Hepatocellular fatty change was observed in rats exposed to 25 ppm or 75 ppm 1,1-DCE intermittently (6 hrs/d, 5 d/wk) for 18 months. This midzonal fatty change was also observed at the 12-month interim sacrifice, but did not appear to progress in severity or incidence over time (Quast *et al.*, 1986). A more severe hepatocellular necrosis and renal tubular necrosis were observed in mice exposed to 55 ppm 1,1-DCE 6 hr/d, 5 d/week for 1 year (Lee *et al.*, 1977).

Uncertainty factors are appropriate due to the limited number of subchronic and chronic inhalation studies (greater 1 year duration) in laboratory animals. In addition, few industrial surveys and epidemiological studies are available on the adverse effects of 1,1-DCE in humans, and these are limited by small sample size, short follow-up, and/or brief exposure periods. But, this limited evidence does suggest an association between repeated exposure to 1,1-DCE and liver damage in humans (EPA, 1976). No toxicokinetic data regarding the absorption, distribution, metabolism or excretion of 1,1-DCE in humans is available.

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CHRONIC TOXICITY SUMMARY

DIETHANOLAMINE

(DEA; 2,2'-Iminodiethanol; 2,2'-Iminobisethanol; Diethylolamine; 2,2'-Aminodiethanol; 2,2'-Dihydroxydiethylamine)

CAS Registry Number: 111-42-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Oral reference exposure level	**0.005 mg/kg-day**
Critical effect(s)	Microcytic anemia, decreased corpuscular hemoglobin and corpuscular volume in rats
Hazard index target(s)	Circulatory system; nervous system

II. Physical and Chemical Properties (Melnick and Tomaszewski, 1990)

Description	Colorless crystals
Molecular formula	$C_4H_{11}NO_2$
Molecular weight	105.14 g/mol
Specific gravity	1.097 @ 20°C
Boiling point	268.8°C @ 760 mm Hg
Vapor pressure	< 0.01 mm Hg @ 20°C
Solubility	soluble in alcohol, water, acetone
Conversion factor	1 ppm = 4.3 mg/m^3 @ 25°C

III. Major Uses and Sources

Diethanolamine is used in the formation of soaps, emulsifiers, thickeners, wetting agents, and detergents in cosmetic formulations (Melnick and Thomaszewski, 1990). It is used as a dispersing agent in some agricultural chemicals, as an absorbent for acidic gases, as a humectant, as an intermediate in the synthesis of morpholine, as a corrosion inhibitor, and as a component in textile specialty agents (Beyer *et al.*, 1983). Diethanolamine is permitted in articles intended for use in production, processing, or packaging of food (CFR, 1981; cited in Melnick and Thomaszewski, 1990). It is also found in adhesives, sealants, and cutting fluids (Melnick and Thomaszewski, 1990).

IV. Effects of Chronic Exposures to Humans

There have been no controlled or epidemiological studies concerning diethanolamine exposure in humans.

V. Effects of Exposures in Animals

Diethanolamine replaces choline in phospholipids (Blum *et al.*, 1972). Systemic toxicity consequently occurs in many tissue types including the nervous system, liver, kidney, and blood system. The direct effects of DEA on the respiratory system are unknown since no subchronic or chronic inhalation studies have been conducted. Effects of DEA on the respiratory system following oral or dermal exposures have also not been examined.

A 13-week drinking water study in rats (10 per sex per group) showed significant dose-dependent hematological changes following exposure to DEA at all concentrations tested (320, 630, 1250, 2500, and 5000 ppm (males); 160, 320, 630, 1250, and 2500 (females)). Hematological effects included decreased hemoglobin and mean corpuscular volume (Melnick *et al.*, 1994a). Similar hematological changes were observed following daily topical treatment. In addition to the hematological effects, female rats also showed dose-dependent spinal cord and medullary demyelination beginning at a drinking water concentration of 1250 ppm DEA. Male rats displayed demyelination beginning at 2500 ppm. Female rats gained significantly less weight than controls beginning at 63 mg/kg/day topical treatment. In a companion drinking water study (Melnick *et al.*, 1994b), mice (10 per sex per group) were exposed to concentrations of 0, 630, 1250, 2500, 5000, and 10,000 ppm DEA and displayed dose-dependent hepatotoxicity, nephrotoxicity, and cardiac toxicity. Daily topical treatment in a separate study resulted in skin lesions in mice. Significant hepatic toxicity was observed at all drinking water concentrations, and skin lesions were observed at all topical doses.

Barbee and Hartung (1979a) found that repeated treatment of rats with 330 mg DEA/kg/day significantly inhibited formation of phosphatidyl choline and phosphatidyl ethanolamine in the liver as compared with control rats. In a subsequent study, Barbee and Hartung (1979b) noted changes in liver mitochondrial activity in rats (4 per group) following exposure to DEA in drinking water for up to 5 weeks. Mitochondrial changes were observed at 42 mg/kg/day after 2 weeks.

Daily oral treatment of male rats with 0, 250, 500, or 750 mg/kg/day for 5 days, or 100 mg/kg/day for 14 days resulted in reduced activities of the liver enzymes microsomal hydroxylase and N-demethylase activities (Foster *et al.*, 1971).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Melnick *et al.* (1994a)
Study population	Rats (female)
Exposure method	Drinking water (*ad libitum*)
Critical effects	Hematological changes (decreased total and mean corpuscular hemoglobin, decreased mean corpuscular volume)
LOAEL	160 mg/L (14 mg/kg/day estimated from water consumption data)
NOAEL	Not observed
Exposure duration	13 weeks
Average exposure concentration	14 mg/kg/day for LOAEL group
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	3,000
Oral reference exposure level	0.005 mg/kg-day
Route-to-route conversion factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	20 $\mu g/m^3$ (4 ppb)

No inhalation studies with diethanolamine were located. The study by Melnick *et al.* (1994a) shows dose-dependent adverse hematological and CNS effects in rats exposed to DEA in drinking water. Similar systemic effects were observed following dermal exposure. The Melnick *et al.* subchronic study was of the longest duration and was the most comprehensive report of the systemic effects of DEA in the literature. However, portal-of-entry effects of DEA have not been examined and should be addressed in future studies since this compound has irritant properties. The data from female rats were used since females were more sensitive than males to the hematologic effects of DEA.

The diethanolamine database is relatively weak. Major areas of uncertainty are the lack of adequate human exposure data, the absence of a NOAEL in the major study, the lack of reproductive and developmental toxicity studies, and the lack of chronic inhalation multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

N,N-DIMETHYLFORMAMIDE

(N-Formyldimethylamine)

CAS Registry Number: 68-12-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 µg/m^3** U.S. EPA-RfC This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Liver dysfunction and respiratory irritation in humans
Hazard index target(s)	Alimentary system, respiratory system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	C_3H_7NO
Molecular weight	73.09
Description	Colorless to very slightly yellow liquid
Boiling point	153° C
Melting point	-61° C
Vapor pressure	3.7 mm Hg @ 25° C
Solubility	Soluble in alcohol, ether, acetone, benzene, and chloroform; miscible with water
Conversion factor	2.99 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Dimethylformamide (DMF) is primarily used as a solvent in the production of polyurethane products and acrylic fibers. It is also used in the pharmaceutical industry, in the formulation of pesticides, and in the manufacture of synthetic leathers, fibers, films, and surface coatings (Howard, 1993; Gescher, 1993; Redlich *et al.*, 1988). DMF may be emitted to the environment as a result of its use in a variety of petrochemical industries (Howard, 1993).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to a DMF for at least one year (mean exposure of 5 years), a statistically significant incidence of hepatic impairment as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances were noted (Cirla *et al.*, 1984).

Other changes that were not statistically significant included increased SGOT and SGPT and enlarged livers. The mean time-weighted average concentration of DMF was 22 mg/m^3. Symptoms of irritation occurring only during work at statistically significantly higher incidences include watery eyes, dry throat, and coughing. Also, the exposed workers reported a reduced sense of smell and dry coughs at home at a statistically significant incidence as compared to controls. Several of the DMF exposed workers also reported alcohol intolerance characterized by a disulfiram-type reaction (facial flushing and palpitations following alcohol ingestion). Alcohol consumption, a potential confounder, was controlled for in the study design.

A similar study was conducted on workers who had been employed in an acrylic acid fiber plant for more than 5 years (Cantenacci *et al.*, 1984). Concentrations to which the workers were exposed were characterized as either an 8-hour TWA of 18 mg/m^3 or an 8-hour TWA of 3 mg/m^3. Measures of liver function including SGOT, SGPT, gamma-glutamyl transferase and alkaline phosphatase levels were not significantly different between exposed and unexposed workers. However, the U.S. EPA cautions that because only 54 matched pairs of workers were examined, the power of this study was not high enough to reliably detect a difference in enzyme levels.

U.S. EPA (1995) states that subjective evidence of liver toxicity such as digestive impairment and alcohol intolerance are often observed at exposures below those which cause clinical changes in liver enzymes. Thus, the symptoms may be more sensitive indicators of hepatic impairment.

Three unexplained cases of small-for-date third trimester intrauterine deaths were observed in a group of women working as quality control analysts in the pharmaceutical industry (Farquhason *et al.*, 1983). This represents a 30% stillbirth rate as compared with the average for the general population of about 0.26%. While the authors concluded that the occurrence of stillbirth in these women was not likely due to chance, the effects cannot be solely attributed to DMF because the women were exposed to other agents in addition to DMF.

V. Effects of Animal Exposure

A developmental toxicity study using three species (mice, rabbits and rats) and four routes of administration (oral, inhalation, dermal and i.p.) identified the rabbit as the most sensitive of the three species. Groups of 15 pregnant rabbits were exposed for 6 hours per day on days 8-20 of gestation to 50, 150, or 450 ppm (150, 449, or 1350 mg/m^3) DMF (Hellwig *et al.*, 1991). Slight maternal toxicity as indicated by non-statistically significant decreases in maternal body weight gain, were observed in the 450 ppm exposure group. An increased number of total malformations per litter was observed in the 450 ppm exposure group. Malformations observed at statistically higher incidences compared to controls included hernia umbilicalis, external variations, pseudoankylosis of the forelimbs, and skeletal variation and retardation. The authors conclude that there was a clear teratogenic effect in rabbits following maternal exposure to 450 ppm DMF and a marginal effect following exposure to 150 ppm DMF. A NOAEL of 50 ppm for fetal and maternal effects was reported. Inhalation exposure to 150 ppm was

calculated by the authors to approximate a daily dose of 45 mg/kg/day, which coincides with previous work on this compound in this species.

VI. Derivation of U.S. EPA Reference Concentration

Study	Cirla *et al.*, 1984; Catenacci *et al.*, 1984
Study population	Occupationally exposed workers
Exposure method	Discontinuous inhalation exposures
Critical effects	Digestive disturbances and slight hepatic changes
LOAEL	22 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day), 5 days/week (assumed)
Average occupational exposure	7.9 mg/m^3 for LOAEL group
Human equivalent concentration	7.9 mg/m^3
Exposure duration	5 years (mean exposure duration)
LOAEL uncertainty factor	3.
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Modifying factors	3 (lack of reproductive toxicity data)
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.03 mg/m^3 (30 $\mu g/m^3$, 0.009 ppm, 9 ppb)

Intermediate uncertainty factors were used for LOAEL and subchronic extrapolation because of the mild nature of the effects observed and the nearly slightly less than chronic exposure duration.

The major strength of the RfC is the availability of human health effects data over several years of exposure. The major uncertainties are the difficulty in estimating exposure patterns and magnitude, the lack of a NOAEL observation, and the lack of complete reproductive and developmental toxicity data.

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CHRONIC TOXICITY SUMMARY

2,4-DINITROTOLUENE

(1-methyl-2,4-dinitrobenzene; 2,4-DNT; 2,4-dinitrotoluol)

CAS Registry Number: 121-14-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**7 μg/m^3**
Oral reference exposure level	**0.002 mg/kg body wt-day**
Critical effect(s)	Incoordination, stiffness and rigid paralysis of limbs and biliary tract hyperplasia in beagle dogs.
Hazard index target (s)	Nervous system; alimentary system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula:	$C_7H_6N_2O_4$
Molecular Weight:	182.14
Description:	yellow to red solid (needles) or yellow liquid; slight odor
Vapor Pressure:	1.4 x 10^{-4} torr at 25°C
Solubility:	Practically insoluble in water (0.03g/100g water at 22°C). Soluble in alcohol, ether, acetone, benzene and pyridine.
Conversion factor:	7.45 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

2,4-Dinitrotoluene (2,4-DNT) is the most prevalent dinitrotoluene isomer (HSDB, 1995). 2,4-DNT is primarily used as an intermediate for the production of toluene-2,4-diamine and toluene diisocyanate, compounds used to produce flexible polyurethane foams. It is also used in the munitions industry as a modifier for smokeless powders, as a plasticizer in moderate and high explosives, and as a waterproofing agent. Release of 2,4-DNT to the environment may occur from any of the above uses. Exposure may occur through the ingestion of drinking water containing 2,4-DNT or from dermal and inhalation exposure in or near an occupational setting where 2,4-DNT is manufactured.

IV. Effects of Human Exposure

Metabolism studies on workers at a dinitrotoluene (DNT) manufacturing plant showed that the most common urinary metabolites (up to 86%) of 2,4-DNT were 2,4-nitrobenzoic acid and 2-amino-4-dinitrobenzoic acid (Turner *et al.*, 1985). Other urinary excretion products included the unchanged parent compound, 2,4-dinitrobenzyl glucuronide, 2-(N-acetyl)amino-4-nitrobenzoic acid and metabolites of the compound 2,6-dinitrotoluene. The elimination of total DNT-related material from urine was rapid, with calculated half-times estimated from 1.0 to 2.7 hr. DNT metabolites were present in low to undetectable concentrations by the start of the next workshift, indicating that accumulation is unlikely. The presence of the metabolite 2-amino-4-nitrobenzoic acid indicates that nitro group reduction by intestinal microflora probably occurs.

Another occupational study of workers at an explosives factory determined dermal exposure to be a major route of absorption (Woollen *et al.*, 1985). Analysis of the major urinary metabolite 2,4-dinitrobenzoic acid showed that uptake of 2,4-DNT is rapid and that the highest levels were normally seen in the end-of-shift specimens.

An early study of 714 workers exposed to dinitrotoluene (including isomers other than 2,4-DNT) used in the manufacture of smokeless powder over a 12-month period recorded a number of symptoms of toxicity (McGee *et al.*, 1947). Symptoms included anemia, cyanosis, weakness, lassitude, headache, inappetence, nausea or vomiting, dizziness, upper abdominal discomfort, and pain or parasthesia in the extremities. Reduction of exposure to dinitrotoluene produced a marked drop in the incidence of symptoms. Exposure levels were not given.

A NIOSH study of 30 workers exposed to dinitrotoluene and diaminotoluene in a chemical plant reported a decrease in sperm counts, a slight change in one category of abnormal sperm and a small, but insignificant, increase in spontaneous abortions for the wives of those exposed (Ahrenholz and Channing, 1980). However, the sperm count in the control group was abnormally high. A comprehensive study of workers at a second plant under similar conditions found no urogenital, reproductive or fertility differences compared to controls (Hamill *et al.*, 1982).

V. Effects of Animal Exposure

Elimination of 2,4-DNT in mice following oral administration (100 mg/kg) was 66% after 8 hours (Schut *et al.*, 1985). Urine was the major route of elimination while elimination via the feces was minimal. Metabolites of 2,4-DNT in rat urine are the same as those found in human urine, with some quantitative differences (Rickert and Long, 1981). The major metabolites excreted by rats are 2,4-dinitrobenzoic acid and 2,4-dinitrobenzyl glucuronide. Biliary metabolites of 2,4-DNT can undergo enterohepatic circulation where they are hydrolyzed and reduced further by intestinal microflora (Rickert *et al.*, 1984; Sayama *et al.*, 1989).

The most comprehensive chronic toxicity study on 2,4-DNT was commissioned by the U.S. Army and consisted of three reports involving exposure in dogs (Ellis *et al.*, 1985), rats (Lee *et al.*, 1985) and mice (Hong *et al.*, 1985). In Part 1, 6 beagle dogs/sex/group were given 0, 0.2, 1.5, or 10 mg/kg day of 2,4-DNT in hard gelatin capsules for up to 2 years (Ellis *et al.*, 1985). Neurotoxicity was the major adverse effect seen in all dogs at the 10 mg/kg dose level by six months and one dog at the 1.5 mg/kg dose level near the end of the study. This effect was characterized by incoordination, stiffness and rigid paralysis in the hind limbs which progressed upwards towards the front limbs and neck in the most severely affected dogs. Similar neurotoxic signs were seen in the lip and tongue. Histopathology revealed vacuolation, endothelial proliferation and gliosis of the cerebellums of some affected dogs. Effects on erythrocytes, including methemoglobin and Heinz bodies (derived from denatured hemoglobin), were seen in the high dose dogs. During the second year of the study, the surviving dogs developed an 'adaptation' to this effect and had normal erythrocytes. Biliary tract hyperplasia, including the gall bladder, was observed in most high dose dogs and in some dogs of the 1.5 mg/kg group. Depressed body weights were noted in the high dose group but the range in weights was large. No other adverse effects were seen. Mild to severe degeneration of the testes was noted in dogs given 25 mg/kg 2,4-DNT in a subchronic range finding study but not in dogs given 10 mg/kg for 2 years during the chronic study.

In the second part of the long-term toxicity study of 2,4-DNT, 38 CD rats/group/sex were given the chemical in their diet for up to 2 years (Lee *et al.*, 1985). Males were fed an average of 0, 0.57, 3.9 or 34 mg/kg/day while females were fed an average of 0, 0.71, 5.1 or 45 mg/kg/day. In the high dose group, cumulative deaths were more than 50% higher than in control rats within the first year of the study. Weight gains were reduced 30-40%. At 12 months, a marked atrophy of seminiferous tubules and depression of spermatogenesis were observed in male rats. Neurotoxic effects, such as the stiff hind-leg gait seen in dogs, occurred in only a few of the high dose rats. Some evidence of anemia was seen in the highest doses, but there was no consistent direct evidence of methemoglobinemia and Heinz bodies as seen in dogs (Ellis *et al.*, 1985) and mice (Hong *et al.*, 1985).

In the third part of the long-term toxicity study of 2,4-DNT, 38 CD-1 mice/group/sex were given an average of 0, 14, 95 and 898 mg/kg/day of the chemical in their diet for up to 2 years (Hong *et al.*, 1985). All high dose males and females died by Month 18 and 21, respectively. A greater than 20% depression in body weight occurred throughout the study in high dose mice compared to control mice. Male mice fed 95 mg/kg/day experienced a greater than 10% decrease in weight compared to controls after 1 year while male mice fed 14 mg/kg/day had close to a 10% decrease in body weight compared to controls at approximately 16 to 21 months. Clinical pathology revealed toxic anemia, methemoglobin and many Heinz bodies present in the high dose mice. Significant increases in spleen and liver weights were recorded at 1 year in mice at this same dose level. All treated mice had an increased dose-related pigment in many tissues, particularly the liver and spleen. High dose females exhibited ovarian atrophy while the 95 mg/kg and high dose males exhibited testicular atrophy. Hepatocellular dysplasia was observed in all treatment groups of male mice but only in the high dose group among female mice.

A subchronic 2,4-DNT feeding study in rats by Kozuka et al (1979) also noted similar neurotoxic effects. Twenty to 23 male Wistar-STD rats fed diets containing 0.5% 2,4-DNT for 6 months developed clinical signs of toxicity including jerky incoordination and decreased spontaneous movements. Assuming male rats consume 4% of their body weight in food per day (based on data in Gold *et al.*, 1984), this dose of 2,4-DNT is equivalent to approximately 200 mg/kg body wt-day. Mortality at the end of the study was 71%. Relative liver, spleen and kidney weights were significantly increased. 'Puruloid' matter was seen in the liver. Testicular atrophy was apparent and relative testes weight was decreased. Methemoglobin in 2,4-DNT-treated rats was 7 times higher than in controls. Serum albumin levels had decreased while activities of nearly all other serum enzymes had increased significantly.

In a male reproductive toxicity study, 9-10 Sprague-Dawley rats/group were fed diets containing 0, 0.1 or 0.2% 2,4-DNT for 3 weeks (Bloch *et al.*, 1988). Assuming male rats consume 4% of their body weight in food per day (based on data in Gold *et al.*, 1984), this dose range is equivalent to approximately 0, 40 and 80 mg/kg body wt-day, respectively. Final body weights were reduced in a dose-dependent manner. At the high dose, epididymal weight, but not testis weight, had decreased significantly. Epididymal sperm reserves were also reduced at this dose level. Ultrastructural changes in Sertoli cell morphology were observed mainly at the high dose level, characterized by swollen mitochondria and distended endoplasmic reticulum. Increased levels of follicle stimulating hormone and luteinizing hormone, but not testosterone, were seen in the high dose group. These results suggest that 2,4-DNT affects pituitary function, alters Sertoli cell structure and appears to affect maturation of spermatozoa.

A developmental/teratogenic study by Price *et al.* (1985) administered 0, 14, 35, 37.5, 75, 100 or 150 mg/kg body wt-day of technical grade DNT (containing about 76% 2,4-DNT, 19% 2,6-DNT, 2.4% 3,4-DNT and less than 3.5% other isomers) by oral gavage on days 7-20 of gestation to pregnant rats. Clinical signs of toxicity were seen in exposed rats. The mortality rate was 46.2% at the highest dose. A dose-related decrease in maternal weight gain and a dose-related increase in relative maternal liver and spleen weight were observed. Increased methemoglobinemia and reticulocytosis and decreased RBC count and hematocrit were observed at the 100 mg/kg body wt-day level. However, fetal development and number of malformations were unchanged compared to controls. Resorptions or late fetal deaths per litter were greater compared to controls at the high dose, but not statistically different. The study found no evidence for teratogenicity of 2,4-DNT at levels that had produced maternal toxicity.

In a 3-generation study, groups of 10-24 Sprague-Dawley rats/sex were fed diets containing approximately 0, 0.75, 5, or 35 mg/kg/day 2,4-DNT for up to 6 months prior to mating (Ellis *et al.*, 1979). Each parental generation produced two sets of offspring. There were only two generations in the high dose group because of the combined effects of the overall toxicity of 2,4-DNT (decreased body weight, general debilitation and antispermatogenesis). Pup survival was reduced and litter size and pup weights were slightly lower, but it was concluded that these effects were due to maternal neglect and aging. Parental fertility and offspring viability were not significantly affected at the other dose levels. Overall, the 3-generation study found no specific reproductive effects of 2,4-DNT.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Ellis *et al.*, 1985
Study population	6 beagle dogs/group/sex, 48 total.
Exposure method	Orally, in hard gelatin capsules (0.2, 1.5 or 10 mg/kg body wt-day
Critical effects	Nervous system; incoordination, stiffness and rigid paralysis in the limbs. Liver; biliary tract hyperplasia.
LOAEL	1.5 mg/kg body wt-day
NOAEL	0.2 mg/kg body wt-day
Exposure continuity	Orally, in capsules once a day, 7 days/week
Exposure duration	2 years
Average experimental exposure	0.2 mg/kg body wt-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.002 mg/kg body wt-day
Route-to-route conversion factor	3.5 mg/m^3 per mg/kg bw-day
Inhalation reference exposure level	0.0009 ppm (0.9 ppb, 0.007 mg/m^3, 7 $\mu g/m^3$)

The most sensitive experimental animal tested thus far to toxicity resulting from long-term 2,4-DNT exposure is the beagle dog. The chronic reference exposure level (REL) is based on neurotoxicity and biliary tract hyperplasia, observed at the mid-dose level of 1.5 mg/kg body wt-day. Effects on erythrocytes, including methemoglobin and Heinz bodies, were seen only at the high-dose level of 10.0 mg/kg body wt-day. Applying uncertainty factors of 10 each to account for interspecies differences and to account for any increased susceptibility of sensitive human populations, an oral REL of 0.002 mg/kg/day was obtained. This value is equivalent to an inhalation REL of 7 $\mu g/m^3$ for humans (assuming a daily respiration rate of 20 m^3 of air, an average body weight of 70 kg, and equal absorption by both routes).

The long-term studies in dogs, rats and mice are supported by subchronic studies which observed most of the same adverse effects following 2,4-DNT exposure. Moreover, the major adverse effects observed in these three animal species (neurotoxicity, methemoglobinemia, Heinz bodies and cyanosis) were qualitatively similar to those effects seen in human poisoning cases. The metabolism of 2,4-DNT also appears to be qualitatively similar in humans and animals.

Ultrastructural changes in male reproductive organs were noted in rats at approximately 20 mg/kg body wt-day in a 3-week study (Bloch *et al.*, 1988). Further research on this aspect of 2,4-DNT toxicity is needed to determine if male reproductive organ toxicity is also a critical effect.

The strengths of the inhalation REL include the availability of chronic exposure data

and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of inhalation exposure studies.

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CHRONIC TOXICITY SUMMARY

1,4-DIOXANE

(Synonym: dihydro-p-dioxin, diethylene dioxide, p-dioxane, glycolethylene ether)

CAS Registry Number: 123-91-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3,000 μg/m^3**
Critical effects	Liver, kidney, hematologic changes in rats
Hazard index target(s)	Alimentary system; kidney; circulatory system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	$C_4C_8O_2$
Molecular weight	88.10 g/mol
Description	Colorless liquid
Vapor pressure	37 mm Hg @ 25^{o}C
Solubility	Miscible with water, aromatic solvent, and oils
Kow	0.537
Conversion factor	3.60 μg/m^3 per ppb at 25^{o}C

III. Major Uses and Sources

1,4-Dioxane (dioxane), a cyclic ether, is used as a degreasing agent, as a component of paint and varnish removers, and as a wetting and dispersion agent in the textile industry. Dioxane is used as a solvent in chemical synthesis, as a fluid for scintillation counting, and as a dehydrating agent in the preparation of tissue sections for histology (Grant and Grant, 1987; HSDB, 1995).

IV. Effects of Human Exposure

Dioxane is absorbed by all routes of administration (HSDB, 1995). In humans, the major metabolite of dioxane is β-hydroxyethoxyacetic acid (HEAA) and the kidney is the major route of excretion (Young *et al.*, 1976). The enzyme(s) responsible for HEAA formation has not been studied, but data from Young *et al.* (1977) indicate saturation does not occur up to an inhalation exposure of 50 ppm for 6 hours. Under these conditions the half-life for dioxane elimination is 59 min (plasma) and 48 min (urine). Although physiologically based pharmacokinetic (PBPK) modeling suggests HEAA is the ultimate toxicant in rodents exposed to dioxane by ingestion, the same modeling procedure does not permit such a distinction for humans exposed by inhalation (Reitz, *et al.*, 1990).

Several anecdotal reports have appeared in which adverse health effects due to chronic dioxane exposure are described. Barber (1934) described dioxane exposed factory workers, some of whom exhibited signs of liver changes, increased urinary protein and increased white blood cell counts, and some of whom died from apparent acute exposures. Although the kidney and liver lesions were considered manifestations of acute exposure, the author suggested a chronic component that was manifested by increased white blood cells. A case was reported in which a worker, who died following exposure by inhalation and direct skin contact to high (unspecified) dioxane levels, exhibited lesions in the liver, kidneys, brain and respiratory system, but the effects could not be easily separated from the effects due to high intake of alcohol (Johnstone, 1959).

In a German study (Thiess *et al.*, 1976 / in German, described in NIOSH, 1977) 74 workers exposed to dioxane in a dioxane-manufacturing plant (average potential exposure duration - 25 years) underwent evaluation for adverse health effects. Air measurements indicated dioxane levels varied from 0.01 to 13 ppm. Clinical evaluations were applied to 24 current and 23 previous workers. Evidence of increased aspartate transaminase (SGOT), alanine transaminase (SGPT), alkaline phosphatase, and gamma glutamyltransferase activities (liver function) was noted in these workers, but not in those who had retired. The indicators of liver dysfunction, however, could not be separated from alcohol consumption or exposure to ethylene chlorohydrin and/or dichloroethane.

A follow-up mortality study was conducted on chemical plant manufacturing and processing workers who were exposed to dioxane levels ranging from < 25 to > 75 ppm between 1954 and 1975 (Buffler *et al.*, 1978). Total deaths due to all causes, including cancer, did not differ from the statewide control group, but the data were not reanalyzed after removing the deaths due to malignant neoplasms. The study is limited by the small number of deaths and the small sample number. The study did not assess hematologic or clinical parameters that could indicate adverse health effects in the absence of mortality.

Yaqoob and Bell (1994) reviewed human studies on the relationship between exposure to hydrocarbon solvents - including dioxane - and renal failure, in particular rare glomerulonephritis. The results of their analysis suggest that such solvents may play a role in renal failure, but dioxane was not specifically discussed. Of interest to the discussion on chronic exposure to dioxane is the suggestion that the mechanism of the disease process involves local autoimmunity with decreased circulating white blood cells (see below).

V. Effects of Animal Exposure

In rats, the major metabolite of dioxane is HEAA which is excreted through the kidneys (Braun and Young, 1977). Exposure to dioxane by ingestion results in saturation of metabolism above 100 mg/kg given in single dose. Saturation of metabolism was also observed as low as 10 mg/kg if dioxane was administered in multiple doses. Dioxane itself is not cleared through the kidney.

A decrease in metabolic clearance with increasing dose (iv) has been interpreted as the saturation of metabolism at the higher doses (Young *et al.*, 1978).

For Sprague-Dawley rats, the metabolic fate of inhaled dioxane (head only exposure) was based on one air concentration (50 ppm). At this level, nearly all the dioxane was metabolized to HEAA since HEAA represented 99 percent of the total dioxane + HEAA measured. The plasma half-life for dioxane under these conditions was 1.1 hours. The absorption of dioxane through the inhalation pathway could not be exactly determined, because of a high inhalation rate (0.24 liters/min), calculated on the basis of complete absorption (Young *et al.*, 1978; U.S. EPA, 1988). Although the high inhalation rate could be dioxane related, another explanation may be the stress incurred when the jugular veins were cannulated as part of the experiment. Extensive absorption by inhalation is also inferred from the high tissue/air partition coefficients (Reitz *et al.*, 1990).

Although the PBPK modeling suggests that in rat the parent dioxane is a better dose surrogate than HEAA for exposure by ingestion, the inhalation modeling did not use more than one inhalation dose. No studies were located on the biological or biochemical properties of HEAA or the properties of the enzyme(s) that are responsible for the transformation of dioxane into HEAA.

Rats (Wistar) were exposed by inhalation to dioxane (111 ppm; 7 hours/day, 5 days/week) for 2 years (Torkelson *et al.*, 1974). Increased mortality and decreased body weight gains, compared to unexposed control rats, were not observed. Among the male rats, decreased blood urea nitrogen (kidney function), decreased alkaline phosphatase (cholestatic liver function), increased red blood cells, and decreased white blood cells were observed. According to the authors, exposure related non-cancerous tissue lesions were not observed during the 2-year period. In another inhalation study, rats were exposed to dioxane at levels of 0.15, 1.3, and 5.7 ppm (Pilipyuk *et al.*, 1978). Frequency was not specified, but the duration is given as “90 successive days”. At the end of the 3-month exposure, increased SGOT activity at the two highest doses and increased SGPT activity at all doses were measured in the sera of the exposed rats. Rats exposed to the highest dose also exhibited increased urinary protein and chloride levels, each of which returned to control levels during an unspecified recovery period. Pilipyuk *et al.* (1978) also report changes in the minimum time (ms) required for an electric stimulus to result in excitation of extensor and flexor muscles. Although Pilipyuk *et al.* (1978) consider the changes to be a reflection of adverse effects due to exposure to dioxane, Torkelson *et al.* (1974) do not consider the hematologic and clinical changes of toxicologic importance. In particular, toxic manifestations are usually associated with increased blood urea nitrogen and alkaline phosphatase levels, whereas these levels decreased in the Torkelson *et al.* (1974) investigation. The reason for the discrepancies between the two studies, in particular the extremely low dioxane exposure levels in the Pilipyuk *et al.* (1978) study, is unknown. One explanation could be the purity of the dioxane used, which was not described in the latter study, although such contamination would be unlikely to account for the large difference in exposure levels.

Kociba *et al.* (1974) exposed rats (Sherman) to dioxane by ingestion of drinking water for up to 2-years. The drinking water levels were 0, 0.01, 0.1, and 1.0 percent, which were converted to daily intake according to measured rates of water consumption during exposure. Exposure to the highest level resulted in decreased body weight gain and increased deaths. According to the

authors, exposure related hematologic changes did not occur. Histopathologic examination revealed evidence of regeneration of hepatic and kidney tissues in rats exposed to 1.0 or 0.1 percent, but not in rats exposed to 0.01 percent dioxane. On the assumption of total absorption of dioxane from the gastrointestinal tract, the exposure levels in female and male rats is as follows: 0.01%-18 ppm/F, 9.3 ppm/M; 0.1% -144 ppm/F, 91 ppm/M.

The teratogenic potential of dioxane was studied in rats (Giavini *et al.*, 1985). Dioxane was administered by gavage at doses of 0, 0.25, 0.5, and 1.0 ml/kg-day, on gestation days 6-15, and observations continued through day 21. Dams exposed to the highest dose exhibited nonsignificant weight loss and a significant decrease in food consumption during the first 16 days. During the remaining 5 days, food consumption increased, but the weight gain reduction in the presence of dioxane continued. At the 1.0 ml/kg-day dose, mean fetal weight and ossified sternebrae were also reduced. The inability to separate the developmental toxicity from maternal or embryotoxicity renders these data inconclusive as to the developmental toxicity of dioxane. If toxicity to the dam and/or embryo exists, the NOAEL for dioxane (based on density = 1.03 gm/ml) is 517 mg/kg-day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Torkelson *et al.* (1974)
Study populations	Rats
Exposure method	Discontinuous inhalation
Critical effects	No effects on liver, kidney, or hematologic function were noted in this study. Such dysfunctions, however, were observed in rats exposed to dioxane by ingestion (Kociba, *et al.*, 1974) and humans (Theiss, *et al.*, 1976 / described by NIOSH, 1977).
LOAEL	Not observed in inhalation studies
NOAEL	111 ppm
Exposure continuity	7 hr/d x 5 days/wk
Average experimental exposure	23 ppm (111 x 7/24 x 5/7)
Human equivalent concentration	23 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	2 years
LOAEL uncertainty factor	1
Subchronic exposure	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.8ppm (80 ppb; 3.8 mg/m^3; 3000 µg/m^3)

The lifetime rat inhalation study of Torkelson *et al.* (1974) is the only detailed inhalation study available in the literature. The Pilipyuk *et al.* (1977) study contains useful and consistent data, but the absence of necessary details prevents the use of these results for the determination of a chronic reference exposure level (REL). Although the ingestion study (Kociba *et al.*, 1974) shows unequivocal toxic responses (liver and kidney) of the rat to dioxane by ingestion, exposure to 111 ppm by inhalation leads to equivocal results (Torkelson *et al.*, 1974). In particular, serum markers for liver and kidney dysfunction decrease in value, whereas toxic responses are associated with increased levels. The lack of toxic hematologic endpoints observed in the ingestion study suggests that toxicity of dioxane may be route of exposure-specific. Hematologic changes were also observed in the early worker study wherein changes in white blood cell count occurred (Barber, 1934), but the directions are different. The studies on humans and rodents therefore suggest inhalation of dioxane may lead to adverse biologic effects, but good dose-response data are not available. A partial explanation may lie in the dose-response characteristic of the metabolism of dioxane, wherein toxicity may be a function of the saturation of metabolism. For inhalation, neither the point of saturation nor the mechanism has been established. Importantly, the end-point for dioxane chronic exposure may not be established.

Although a free-standing NOAEL is not a desirable parameter to use for the development of a chronic REL, other studies support the conclusion that exposure to dioxane leads to adverse health effects. These observations have been documented among experimental animals (Kociba *et al.*, 1974; Pilipyuk *et al.*, 1977) and humans (Thiess, *et al.*, 1976, described in NIOSH, 1977). Until additional data from inhalation dose-response studies become available, a chronic REL based on the free-standing NOAEL is considered the best available.

The strength of the REL is that it is based on a full lifetime study, with a large number of toxic endpoints and a good sample size. The weaknesses include use of a free standing NOAEL, the limited human data, and the lack of developmental studies.

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CHRONIC TOXICITY SUMMARY

EPICHLOROHYDRIN

(1-chloro-2,3-epoxy-propane)

CAS Registry Number: 106-89-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 μg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effects	Histological changes in nasal turbinates in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (from HSDB, 1994, except as noted)

Description	Colorless
Molecular formula	C_3H_3ClO
Molecular weight	92.5
Specific gravity	1.181 @ 20° C
Boiling point	117.9° C
Vapor pressure	13 mm Hg @ 20° C
Solubility	Slightly soluble in water, soluble in most organic solvents
Conversion factor	1 ppm = 3.78 mg/m^3 @ 25° C

III. Major Uses and Sources

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins. It is also used as a solvent and is used in the synthesis of glycerol. Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994).

IV. Effects of Exposures to Humans

Studies of male reproductive function have shown no evidence of decreased sperm counts in populations occupationally exposed to epichlorohydrin (Milby *et al.*, 1981).

V. Effects of Exposures in Animals

Rats were exposed for 136 weeks (6 hours/day, 5 days/week) to 0, 10, 30, or 100 ppm (0, 38, 113, or 380 mg/m^3) epichlorohydrin (Laskin *et al.*, 1980). Kidney damage in the form of renal tubular degeneration and dilatation was observed in rats exposed to 30 ppm or greater. Severe inflammation was observed in the nasal passages of 90% of the control animals in addition to the treated animals, thus preventing comparison of this effect between the two groups.

A subchronic exposure of rats to 9, 17, 27, 56, or 120 ppm (34, 64, 102, 212, or 454 mg/m^3) for 6 hours/day, 5 days/week for 11-19 exposures showed evidence of extrarespiratory effects, including liver congestion and necrosis and tubular atrophy in the kidneys at the highest concentration (Gage, 1959). Lethargy and weight loss were observed at 56 ppm.

A study on the effects of epichlorohydrin exposure for 10 weeks (6 hours/day, 5 days/week) on male and female fertility in rats rabbits showed that male rats exposed to 50 ppm (189 mg/m^3) were significantly less fertile as measured by successful matings to unexposed females (John *et al.*, 1979; 1983a). No histological changes were observed in the testes of the male rats at the end of exposure. No significant effects on fertility occurred in the exposed female rats. Degenerative changes in the nasal epithelium were observed in the female rats exposed to 25 ppm (94.5 mg/m^3), and in both sexes at 50 ppm.

A teratology study in rats and rabbits exposed to 0, 2.5, or 25 ppm (0, 9.5, or 95 mg/m^3) 7 hours/day during the critical days of gestation showed no significant differences between controls and treated animals in the incidence of developmental defects, maternal toxicity, or in histopathology of the lungs, nasal turbinates, or trachea (John *et al.*, 1983b).

Mice and rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 190 mg/m^3) epichlorohydrin for 6 hours/day. 5 days/week for 90 days (Quast *et al.*, 1979). Animals were observed for clinical signs of toxicity and were measured biweekly for body weight changes. Body weight measurements, clinical chemistry, hematology, and urinalysis were conducted. Gross and histopathological examinations were performed at the end of the experiment. Exposures of rats to 25 and 50 ppm epichlorohydrin resulted in inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates. No adverse effects were observed in rats exposed to 5 ppm (19 mg/m^3). Mice similarly showed focal erosion, hyperplasia and metaplasia in the epithelium of the nasal turbinates when exposed to 25 ppm or greater.

VI. Derivation of U.S. EPA RfC

Study	Quast *et al.* (1979); U.S. EPA (1994)
Study population	Rats and Mice (10 per sex per concentration)
Exposure method	Discontinuous whole-body inhalation
Critical effects	Inflammation, focal erosions, hyperplasia, and metaplasia
LOAEL	25 ppm (94.5 mg/m^3)
NOAEL	5 ppm (19 mg/m^3)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	90 days
Average experimental exposure	0.89 ppm
Human equivalent concentration	0.095 ppm (gas with extrathoracic respiratory effects, RGDR = 0.11, based on MV = 0.14 L, SA(ET) = 11.6 cm^2)
LOAEL factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0003 ppm (0.3 ppb; 0.001 mg/m^3; 1 $\mu g/m^3$)

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies limited reproductive toxicity data, and the small groups tested in the study.

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CHRONIC TOXICITY SUMMARY

1,2-EPOXYBUTANE

(1-butene oxide; 1,2-butene oxide; 1,2-butylene oxide; 1,2-epoxybutane; 2-ethyloxirane; ethylethylene oxide; NCI-C55527)

CAS Registry Number: 106-88-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Degenerative lesions of the nasal cavity in mice
Hazard index target(s)	Respiratory system; circulatory system

II. Physical and Chemical Properties (HSDB, 1994)

Molecular formula	C_4H_80
Molecular weight	72.12 g/mol
Specific gravity	0.837 ° C
Boiling point	63.3° C
Vapor pressure	176 mm Hg 25° C
Solubility	Soluble in ethanol, ether, acetone, water
Odor threshold	Unknown
Description	Colorless liquid/gas
Conversion factor	1 ppm = 2.95 mg/m^3

II. Major Uses or Sources

Epoxy butane is used as a chemical intermediate, acid scavenger, and stabilizer for chlorinated solvents (Reprotext, 1994). It is highly reactive and flammable undergoing exothermic polymerization reactions in the presence of acids, bases and some salts. It is less volatile than ethylene or propylene oxide (Reprotext, 1994).

III. Effects of Human Exposure

No human toxicological data were found for 1,2-epoxybutane.

IV. Effects of Animal Exposure

F344/N rats (50/sex) were exposed to 0, 200, or 400 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival was impaired and concentration-related increases of inflammation, respiratory epithelial hyperplasia, olfactory sensory epithelial atrophy, and hyperostosis of the nasal turbinate bone cavity were observed in male and female rats exposed to either concentration.

B6C3F1 mice (50/sex) were exposed to 0, 50, or 100 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival and body weight gain were reduced significantly at 100-ppm in both sexes. Significant concentration-related increases in incidence of chronic inflammation, epithelial hyperplasia, and erosion were noted in both sexes at either concentration. Increases in granulocytic hyperplasia and splenic hematopoiesis were noted at both concentrations in female mice.

Male and female mice exposed to 800 ppm (2360 mg/m^3) EBU for 6 hours/day, 5 days/week, for 13 weeks were listless after the first exposure (NTP, 1988). Animals from this group all died by the end of the 1 3-week exposure. Renal tubular necrosis, thymic and splenic atrophy was seen in mice exposed to 800 ppm; decreased liver weights were observed following exposure of mice to 400 ppm (1180 mg/m^3) or more. Inflammation of the nasal turbinates was seen in female mice exposed to 100 ppm (295 mg/m^3) or more. No inflammation was observed in controls.

Miller *et al.* (1981) exposed rats and mice of either sex to 0, 75, 150, or 600 ppm (0, 221, 442, or 1770 mg/m^3) EBU 6 hours/day, for 5 days/week. In this study, no treatment-related effects were noted except for histological lesions in the nasal mucosal epithelium and reduced specific gravity in the urine of rats treated with 600 ppm.

Wolf (1961) observed increased lung weights in rats exposed to 800 ppm of a mixture of epoxybutane isomers. No increase in lung weight was seen at 400 ppm.

Sikov *et al.* (1981) conducted experiments to determine the reproductive toxicity of EBU in rats and rabbits. Rats were exposed to 0, 250, or 1000 ppm (0, 738, or 2950 mg/m^3) 1,2-epoxybutane for 7 hours/day, 5 days/week for 3 weeks prior to gestation, or for 7 hours/day on days 1-19 of gestation. Maternal toxicity in the form of 10% weight loss was observed in rats exposed to 1000 ppm. One death out of 42 occurred in the dams exposed to 1000 ppm. No adverse histological, reproductive, or developmental effects were seen at any concentration. Exposure of rabbits to the same concentrations as in the rat experiment on days 1-24 of gestation showed more severe effects at lower concentrations than those observed in rats. In the rabbits, 6 out of 48 dams died during exposure to 250 ppm, and 14 out of 24 died at 1000 ppm. Extensive maternal mortality in this study prevented evaluation of the reproductive and developmental effects.

V. Derivation of U.S. EPA RfC

Study	National Toxicology Program (NTP, 1988); U.S. EPA, 1994
Study population	Rats and mice
Exposure method	Discontinuous inhalation
Critical effects	Damage to the upper respiratory epithelium was observed in both species at all concentrations. Mice also showed an increased incidence of granulocytic hyperplasia and splenic hematopoiesis at both concentrations, possibly due to inflammation in the upper respiratory tract
LOAEL	50 ppm (mice)
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Average experimental exposure	8.9 ppm for LOAEL group
Human equivalent concentration	1.7 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.18, based on MV = 0.06 L, SA(ET) = 2.9 cm^2)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm (6 ppb; 0.02 mg/m^3; 20 $\mu g/m^3$)

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of adequate human exposure data, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

ETHYL CHLORIDE

(Chloroethane; monochloroethane; ether hydrochloric)

CAS Registry Number: 75-00-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**10,000 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Delayed fetal ossification in mice
Hazard index target(s)	Teratogenicity; alimentary system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas
Molecular formula	C_2H_5Cl
Molecular weight	64.52
Specific gravity	0.9214 @ 0°C
Boiling point	12.3 °C
Melting point	-138.7 °C
Vapor pressure	1000 mm Hg @ 20 °C
Conversion factor	1 ppm = 2.64 mg/m^3 @ 25°C

III. Major Uses or Sources

Ethyl chloride is used as a starting point in the production of tetraethyl lead and as a refrigerant, solvent and alkylating agent (HSDB, 1995). It is also used as a topical anesthetic (Clayton and Clayton, 1994).

IV. Effects of Human Exposure

Neurological symptoms have been observed in human case-studies in instances of ethyl chloride abuse. Cerebellar-related symptoms including ataxia, tremors, speech difficulties, and hallucinations were observed in a 28-year old female who had sniffed 200-300 ml. ethyl chloride off her sleeve daily for 4 months (Hes *et al.* 1979). The patient's liver was enlarged and tender. Four weeks following cessation of exposure, all symptoms were absent.

V. Effects of Animal Exposure

Pregnant mice were exposed to 1300, 4000, or 13000 mg/m^3 ethyl chloride in air for 6 hours per day on days 6-15 of gestation (Scortichini *et al.*, 1986). No effects on fetal resorptions rates, litter size or body weight or maternal health were observed. A statistically significant increase in the incidence of delayed ossification of the skull bones was observed in fetuses from the 13,000 mg/m^3 ethyl chloride exposed group. This skull effect was accompanied by an non-significant increased incidence of cervical ribs (a supernumerary rib considered to be a malformation). No significant adverse effects were observed in fetuses from the 4000 mg/m^3 exposure group.

No significant adverse effects were observed in rats and mice exposed to 0 or 15000 ppm ethyl chloride for 6 hours per day, 5 days per week for 102 weeks (rats) or 100 weeks (mice) (NTP, 1989). At necropsy, a complete histopathologic examination failed to identify evidence of toxicity. The same study also exposed rats and mice to 2500, 5000, 10,000 or 19,000 ppm ethyl chloride 6 hours per day, 5 days per week for 13 weeks. No exposure-related clinical signs of toxicity or histological changes were observed in exposed animals.

Increased relative liver weights and a slight increase in hepatocellular vacuolation were observed in mice exposed to 5000 ppm ethyl chloride 23 hours per day for 11 days (Landry *et al.*, 1989). No effects were observed in mice exposed to 0, 250, or 1250 ppm ethyl chloride for the same period.

Following acclimatization to an inhalation chamber, two groups of 10 female mice were exposed to 0 or 15,000 ppm ethyl chloride 6 hours per day for 2 weeks (Breslin *et al.*, 1988). Groups of five male mice were housed in each inhalation chamber to synchronize and promote regular cyclicity. The mean length of the estrous cycle in control mice remained constant at 4.5 days during both pre-exposure and exposure periods. Mice in the 15,000 ppm exposure group showed a 0.6 day increase in the mean cycle length during exposure (5.6 days) when compared to the pre-exposure period (5.0 days). The authors attribute this increase in estrous cycle length to a general stress response although they note that it does not preclude direct effects on neuroendocrine function.

Cardiac sensitization to epinephrine in dogs resulting from acute exposure to anesthetic concentrations of ethyl chloride has been reported (Haid *et al.*, 1954; Morris *et al.*, 1953).

VI. Derivation of U.S. EPA RfC

Study	Scortichini *et al.*, 1986; U.S. EPA, 1995
Study population	Mice
Exposure method	Discontinuous whole-body inhalation (on days 6-15 of gestation)
Critical effects	Delayed ossification of skull foramina
LOAEL	13,000 mg/m^3
NOAEL	4,000 mg/m^3
Exposure continuity	6 hours per day
Exposure duration	Days 6-15 of gestation
Average experimental exposure	1,000 mg/m^3 for NOAEL group
Human equivalent concentration	1,000 mg/m^3 for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	10 mg/m^3 (10,000 $\mu g/m^3$; 30 ppm; 30,000 ppb)

The RfC is based on a subacute developmental toxicity study. In accordance with U.S. EPA methodology, a time-weighted average concentration for the discontinuous exposure experiment was not used since the key effect was developmental toxicity. The database deficiencies leading U.S. EPA to employ a modifying factor include the lack of a multigenerational reproductive study.

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis, and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies.

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CHRONIC TOXICITY SUMMARY

ETHYLBENZENE

(Phenylethane; NCI-C56393)

CAS Registry Number: 100-41-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1000 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Developmental toxicity in rabbits and rats
Hazard index target(s)	Teratogenicity; alimentary system; kidney

II. Physical and Chemical Properties (HSDB, 1994)

Molecular formula	C_8H_{10}
Molecular weight	106.16 g/mol
Description	colorless gas
Specific gravity	0.867 @ 20°C
Boiling point	136.2° C
Vapor pressure	10 mm Hg @ 25.9°C
Solubility	soluble in ethanol and ether, partially soluble in water
Conversion factor	1 ppm = 4.35 mg/m^3

III. Major Uses or Sources

Ethylbenzene is used as a precursor in the manufacture of styrene (HSDB, 1994). It is also used in the production of synthetic rubber, and is present in automobile and aviation fuels. It is found in commercial xylene (Reprotext, 1994).

IV. Effects of Human Exposure

Studies on the effects of workplace exposures to ethylbenzene have been complicated by concurrent exposures to other chemicals, such as xylenes (Angerer and Wulf, 1985). Bardodej and Cirek (1988) reported no significant hematological or liver function changes in 200 ethylbenzene production workers over a 20-year period.

V. Effects of Animal Exposure

Rats and mice (10/sex/group) were exposed to 0, 100, 250, 500, 750, and 1000 ppm (0, 434, 1086, 2171, 3257, and 4343 mg/m^3) 6 hours/day, 5 days/week for 90 days (NTP, 1988; 1989; 1990). Rats displayed significantly lower serum alkaline phosphatase in groups exposed to 500 ppm or higher. Male rats had dose-dependently increased liver weights beginning at 250 ppm, while this effect was not seen until 500 ppm in the females. An increase in relative kidney weights was seen in the 3 highest concentrations in both sexes. Minimal lung inflammation was observed in several of the treatment groups, but this phenomenon was attributed to the presence of an infectious agent rather than to ethylbenzene exposure. The mice in this study did not show any treatment-related effects except for elevated liver and kidney weights at 750 and 100 ppm, respectively.

Rats (17-20 per group) were exposed to 0, 600, 1200, or 2400 mg/m^3 for 24 hours/day on days 7 to 15 of gestation (Ungvary and Tatrai, 1985). Developmental malformations in the form of "anomalies of the uropoietic apparatus" were observed at the 2400 mg/m^3 concentration. Skeletal retardation was observed in all exposed groups compared with controls. The incidence of skeletal abnormalities increased with higher concentrations of ethylbenzene.

Rabbits exposed by these investigators to the same concentrations as the rats on days 7 to 15 of gestation, exhibited maternal weight loss with exposure to 1000 mg/m^3 ethylbenzene. There were no live fetuses in this group for which abnormalities could be evaluated. No developmental defects were observed in the lower exposure groups.

Rats (78-107 per group) and rabbits (29-30 per group) were exposed for 6 or 7 hours/day, 7 days/week, during days 1-l9 and 1-24 of gestation, respectively, to 0, 100, or 1000 ppm (0, 434, or 4342 mg/m^3) ethylbenzene (Andrew *et al.*, 1981). No effects were observed in the rabbits for maternal toxicity during exposure or at time of necropsy. Similarly, no effects were seen in the fetuses of the rabbits. The only significant effect of ethylbenzene exposure in the rabbits was a reduced number of live kits in the 1000 ppm group. A greater number and severity of effects were seen in rats exposed to 1000 ppm ethylbenzene. Maternal rats exposed to 1000 ppm exhibited significantly increased liver, kidney, and spleen weights compared with controls. Fetal rats showed an increase in skeletal variations at the 1000 ppm concentration, but the results of the 100 ppm exposure were not conclusive.

Clark (1983) found no significant effects on body weight, food intake, hematology, urinalysis, organ weights or histopathology in rats (18 per group) exposed to 100 ppm (434 mg/m^3) ethylbenzene for 6 hours/day, 5 days/week, for 12 weeks.

Degeneration of the testicular epithelium was noted in guinea pigs and a rhesus monkey exposed to 600 ppm (2604 mg/m^3) for 6 months (Wolf *et al.*, 1956). No effects were reported for female monkeys exposed to the same conditions.

Cragg *et al.* (1989) exposed mice and rats (5/sex/group) to 0, 99, 382, and 782 ppm (0, 430, 1659, and 3396 mg/m^3) 6 hours/day, 5 days/week for 4 weeks. Some evidence of increased salivation and lacrimation was seen in the rats exposed to 382 ppm. No other gross signs of toxicity were observed. Both male and female rats had significantly enlarged livers following exposure to 782 ppm. Female mice also showed a significant increase in liver weight at this concentration. No histopathological lesions were seen in the livers of these mice.

Dose-dependent induction of liver cytochrome P450 enzymes in rats by ethylbenzene was observed by Elovaara *et al.* (1985). Rats (5 per group) were exposed to 0, 50, 300, or 600 ppm (0, 217, 1302, or 2604 mg/m^3) ethylbenzene for 6 hours/day, 5 days/week for 2, 5, 9, or 16 weeks. Cytochrome P450 enzyme induction, and microscopic changes in endoplasmic reticulum and cellular ultrastructure was evident at all ethylbenzene concentrations by week 2, and persisted throughout the exposure. Liver weights were not elevated in these studies.

VI. Derivation of U.S. EPA RfC

Study	U.S. EPA, 1995; Andrew *et al.*, 1981; Hardin *et al.*, 1981
Study population	Rats (78-107 per group) and rabbits (29-30 per group)
Exposure method	Discontinuous inhalation
Critical effects	Skeletal abnormalities in offspring, maternal hepatomegaly and enlarged kidney and spleen (rats). Reduced number of live kits (rabbits).
LOAEL	1,000 ppm
NOAEL	100 ppm
Exposure continuity	6 or 7 hours/day, 5 days/week
Exposure duration	days 1-19 of gestation (rats); 1-24 (rabbits)
Average experimental exposure	100 ppm for NOAEL group (per daily exposure period considered by U.S. EPA)
Human equivalent concentration	100 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	10 (database deficiencies)
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.3 ppm (300 ppb; 1 mg/m^3; 1,000 µg/m^3)

The RfC is based on a subacute developmental toxicity study. The NOAEL in the study was 100 ppm, and the LOAEL was 1000 ppm. Other studies discussed above (e.g. NTP, 1988, 1989,

1990) identify higher concentrations as NOAELs, but do not measure developmental toxicity. The study by Ungvary and Tatrai (1985) reported a NOAEL of 600 mg/m^3 for developmental and maternal effects in several species. However, the reporting and general quality of this paper creates a loss of confidence in its results.

In accordance with U.S. EPA methodology, a time-weighted average concentration for the discontinuous exposure experiment was not used since the key effect was developmental toxicity. The database deficiencies leading U.S. EPA to employ a modifying factor include the lack of a multigenerational reproductive study.

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis, and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies.

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